TABLE OF CONTENTS

| PR | EFA | CExvii |
|-----|-------|---|
| ΑC | CKNC | DWLEDGEMENTSxxi |
| LI | ST O | F CONTRIBUTORSxxv |
| LIS | ST OI | F FIGURESxxxi |
| LIS | ST OI | F TABLESxxxiii |
| LI | ST Ol | F BOXESxxxvii |
| | | DUCTION: CONCEPTS IN THE RELATIONSHIP NGENITAL DISEASES WITH THE ENVIRONMENT |
| Р. | NICC | DLOPOULOU-STAMATI |
| Su | mmai | y1 |
| 1. | Intro | duction2 |
| 2. | The | changing concepts of environmental influences in the causation |
| of | | enital anomalies |
| 3. | Meth | nods to study congenital anomalies and their links to the environment4 |
| | | EUROCAT: Surveillance of environmental impact |
| | | Endpoints for prenatal exposures in toxicological studies |
| | | Evidence from wildlife 5 Epidemiology 6 |
| | | Clinical teratology 6 |
| 4. | | nicals and exposure conditions associated with congenital anomalies7 |
| | 4.1. | Congenital diseases related to environmental exposure to dioxins |
| | | Association of intra-uterine exposure with drugs: the thalidomide effect |
| | 4.3. | Endocrine disrupter exposure and male congenital malformations |
| | 4.4. | Links between in utero exposure to pesticides and their effects |
| | 1 5 | on human progeny. Does European pesticide policy protect health?9 |
| _ | | Phthalates 9 |
| 5. | | ronmental congenital anomalies |
| | | Testicular dysgenesis syndrome |

| | 5.3. | Environmental impact on congenital diseases: | 1.1 |
|------------|--------|---|-----|
| , | D 11 | the case of cryptorchidism | |
| 0. | | cy aspects | 12 |
| | 6.1. | Raising awareness of information society on impact of EU policies and deployment aspects | 12 |
| | 6.2. | The concerns of NGO's related to congenital diseases | 12 |
| | | Environmental impacts on congenital anomalies – information | |
| | | for the non-expert professional | 13 |
| 7. | Con | clusions | 13 |
| | Refe | erences | 14 |
| <u>S</u>] | EC] | TION 1: METHODS | |
| Εľ | NDPO | DINTS FOR PRENATAL EXPOSURES IN TOXICOLOGICAL | |
| | UDI | | |
| | | NTOVANI AND F. MARANGHI | |
| Su | mma | ry | 21 |
| 1. | Intro | oduction | 22 |
| 2. | An c | overview of regulatory tests in developmental toxicology | 24 |
| | 2.1. | Prenatal development toxicity study (OECD guideline 414) | 24 |
| | | Two-generation reproduction toxicity study (OECD 416) | |
| | | In vitro alternative tests for developmental toxicity | 28 |
| | 2.4. | Developmental toxicity testing of environmental contaminants. The example of endocrine disrupters. | 30 |
| 3 | Reco | ommendations for further research in developmental toxicology | |
| | | /ledgements | |
| | | ces | |
| ΙζĊ | 101011 | UCS | 32 |
| EF C(| FEC | ENITAL DEFECTS OR ADVERSE DEVELOPMENTAL TS IN VERTEBRATE WILDLIFE: THE WILDLIFE-HUMAN ECTION | |
| | | y | 27 |
| | | • | 3 / |
| 1. | | duction: The animal – human connection and epigenetic ogramming | 3.8 |
| 2 | _ | mary of pollutant-related defects reported in wildlife | |
| ۷. | | Fish | |
| | ∠.1. | 2.1.1. Deformities of sex-linked structures in fish | |
| | | 2.1.2. Poor reproductive success / reduced hatching in fish | |
| | | 2.1.3. Thyroid disruption in fish | 47 |

| | | 2.1.5. Altered osmoregulation in migrating fish | 48 |
|----|-------|---|----|
| | 2.2. | Birds | 48 |
| | | 2.2.1. Abnormal VTG production in male birds | 49 |
| | | 2.2.2. Deformities of the reproductive tract, and ovo-testes in birds | 49 |
| | | 2.2.3. Embryonic mortality and reduced reproductive success | |
| | | in birds | |
| | | 2.2.4. Altered thyroid function in birds. | |
| | | 2.2.5. Immunosuppression in birds | |
| | | 2.2.6. Eggshell thinning in birds | |
| | 2.2 | 2.2.7. Deformities of the bill and bone in birds | |
| | 2.3. | Reptiles | |
| | | 2.3.2. Effects on turtles | |
| | 2.4. | | |
| | | Mammals | |
| | 2.5. | 2.5.1. Feral rodents | |
| | | 2.5.2. Otters | |
| | | 2.5.3. Mink | 58 |
| | | 2.5.4. Seals and sea lions: Reproductive problems, | |
| | | immunosuppression, adrenal and other effects in seals | |
| | | 2.5.5. Whales and other cetaceans | |
| | | 2.5.6. Polar bears | |
| | | 2.5.7. Black and brown bears | |
| | | 2.5.8. Florida panther | |
| | | 2.5.9. Sitka black tail deer | |
| | | 2.5.10.White tailed deer | |
| | | 2.5.11.Mule deer | |
| | | 2.5.12.Eland | |
| 3. | Sum | mary of some effects found in both humans and wildlife | |
| | 3.1. | · · · · · · · · · · · · · · · · | |
| | 3.2. | | |
| | | Immunotoxicity | |
| 4 | | | |
| | | clusions | |
| Re | feren | ces | 72 |
| | | Way a gya Li Marwya Ba | |
| | | MIOLOGICAL METHODS | |
| | | ANO AND E. ROBERT-GNANSIA | |
| | | y | |
| | | duction | |
| 2. | Sour | ces of data, coding and classification | 92 |

| | 2.1. | Source of data for congenital anomalies | 92 |
|----|--------|---|-------|
| | 2.2. | Coding and classification of congenital anomalies | 93 |
| | | Accuracy of diagnosis and ascertainment of congenital anomalies | |
| | | Source of data, coding and assessment of environmental exposures | |
| 3. | Stud | y designs | 9´ |
| | | Cohort or follow-up study | |
| | | Case-control studies | |
| | 3.3. | Ecological designs | |
| | | 3.3.1. Exploratory studies | |
| | | 3.3.2. Multiple-group comparison study | |
| | | 3.3.3. Space-time cluster study | |
| | | Case reports. | |
| 4. | | etic epidemiology | |
| | | Study designs in genetic epidemiology | 110 |
| | | lems in environmental epidemiology when studying its effects | |
| on | | duction | |
| | | Living status of cases | |
| | 5.2. | Genetic susceptibility | 115 |
| | | Rare diseases, low-level exposures, and small effects | |
| | | Sources of errors | |
| 6 | | Plusions | |
| | | ces | |
| Ν¢ | ieren | ices | 123 |
| | maa | CAM CAMPAINER A ANCH OF ENVIRONMENTAL ANCH OF | |
| | | CAT: SURVEILLANCE OF ENVIRONMENTAL IMPACT | |
| | DOL | | |
| | | y | |
| | | OCAT: What and why? | |
| 2. | The p | prevalence of congenital anomalies | . 134 |
| 3. | Envi | ronmental causes of congenital anomalies | . 135 |
| 4. | EUR | OCAT surveillance of environmental impact | . 137 |
| | 4.1. | Approaches to surveillance | . 137 |
| | | 4.1.1. Assessment of trends in congenital anomaly prevalence | |
| | | 4.1.2. Routine detection of and response to clusters without a well | |
| | | defined a priori exposure hypothesis | |
| | | 4.1.3. Systematic evaluation of environmental exposures | |
| | 4.2. | Envirovigilance | . 141 |
| Re | ferenc | ^es | 1/12 |

| CLINICAL TERATOLOGY |
|---|
| M. CLEMENTI AND E. DI GIANANTONIO |
| Summary |
| 1. Introduction |
| 2. Teratogens |
| 2.1. Basic principles of clinical teratology |
| 2.1. Basic principles of chinical teratology |
| 2.3. Pharmacokinetics in pregnancy |
| 2.4. Methods to identify human teratogens |
| 2.5. Classification of drugs used in pregnancy |
| 2.6. Criteria for proof of human teratogenicity |
| 2.7. Teratogen Information Services (TIS) in Europe |
| 3. Conclusions |
| References |
| |
| |
| SECTION 2 : TERATOGENS |
| |
| DIOXINS AND CONGENITAL MALFORMATIONS |
| |
| J.G. KOPPE, M. LEIJS, G. TEN TUSSCHER AND P.D. BOER |
| Summary |
| 1. Introduction |
| 2. Acute dioxin poisoning |
| 2.1. Animal studies |
| 2.2. Acute dioxin toxicity in man |
| 2.2.1. Yushchenko |
| 2.2.2. Two secretaries |
| 2.3. Hormones |
| 2.4. Thrombocytopenia |
| 3. Hotspots of dioxin pollution |
| 3.1 Amsterdam Diemerzeedijk 1961-1973 |
| 3.2 Yusho-disaster 1968 |
| 3.3 Yucheng-disaster 1978 |
| 3.4 Seveso-disaster 1976 |
| 3.5 Vietnam: Agent Orange spraying 1962-1971 |
| 3.6 Bashkortostan: 1965-1985 |
| 3.7. Chapaevsk 1967-1987 |
| 3.7.1. Prematurity |
| 3.7.2. Intra-uterine growth retardation |
| 3.7.3. Congenital morphogenetic conditions |
| 3.7.4. Congenital malformations |
| 3.7.5. Congenital hydrocephaly without spina bifida |

| | | 3.7.6. | Increasing type 1 diabetes | 17 |
|-----|--------|---------------|--|-------|
| 4. | The: | | vitamin A | |
| | | | | |
| | | | | |
| | 701011 | · · · · · · · | | / |
| T.T | NKS | BETU | VEEN IN UTERO EXPOSURE TO PESTICIDES | |
| | | | TS ON THE HUMAN PROGENY. DOES EUROPEAN | |
| | | | POLICY PROTECT HEALTH? | |
| C. | WAT | TIEZ | | |
| Su | ımmaı | "V | | 18 |
| | | - | n | |
| | | | disorders | |
| ۷. | 2.1. | _ | enital malformations | |
| | 2.1. | | Several birth defects | |
| | | | Central nervous system defects | |
| | | | Cardiovascular defects | |
| | | | Orofacial clefts | |
| | | | Urogenital defects | |
| | | | Limb defects | |
| | 2.2. | | r congenital disorders | |
| | | 2.2.1. | Intrauterine growth retardation | 19: |
| | | 2.2.2. | Neurodevelopmental impairments | . 19. |
| 3. | Does | s Europ | pean pesticide policy protect our health? | . 19 |
| | 3.1. | The p | lant protection product authorisation directive | . 19 |
| | | 3.1.1. | Regulatory testing shortcomings | . 19 |
| | | 3.1.2. | No consideration for combined effects | . 19 |
| | | 3.1.3. | Toxic properties of the formulated products are not properly | |
| | | | evaluated | |
| | | | No systematic review of the scientific literature is required | . 19 |
| | | 3.1.5. | No exclusion criteria are defined for active substances, based | 10 |
| | | 216 | on intrinsic properties | |
| | | | Exposure evaluation deficits | . 199 |
| | | 3.1./. | The substitution principle and comparative assessment are not considered | 100 |
| | 3.2. | The t | hematic strategy on the sustainable use of pesticides | |
| 4 | - | | S | |
| | foren | | 5 | |

| WITH CONGENITAL DEFECTS: THE THALIDOMIDE EFFECT | ŗ |
|--|--------------------------|
| M. CLEMENTI, K. LUGWIG AND A. ANDRISANI | |
| Summary | 207 |
| 1. Introduction | |
| 2. Pharmacokinetics | 209 |
| 3. Mechanism of action | 210 |
| 4. Thalidomide side-effects | 212 |
| 5. "New" indications | 213 |
| 5.1. Leprosy | 215 |
| 5.2. Human Immunodeficiency Virus (HIV) | |
| 5.3. Beucet disease | |
| 5.5. Cancer complications | |
| 6. STEPS programme (System for thalidomide education and prescribin safety) | g |
| 7. Lessons for environmental teratology | |
| 8. Conclusions | |
| References | 218 |
| SECTION 3: CONGENITAL DISEASES ENDOCRINE DISRUPTER EXPOSURE AND MALE CONGENIT MALFORMATIONS | AL |
| M.F. FERNÁNDEZ AND N. OLEA | |
| | |
| | 225 |
| Summary | |
| Summary | 226 |
| Summary | 226 227 |
| Summary | 226 227 232 |
| Summary | 226 227 232 235 |
| Summary | |
| Summary | |
| Summary | |

| 2. | Semen quality and testicular cancer | . 246 |
|----|--|-------|
| 3. | Birth rates of cryptorchidism and hypospadias | . 247 |
| 4. | Discussion | . 248 |
| A | cknowledgements | . 249 |
| | eferences | |
| | | |
| Eľ | NDOCRINE DISRUPTERS, STEROIDOGENESIS | |
| | ND INFLAMMATION | |
| | SVECHNIKOV, V. SUPORNSILCHAI, I. SVECHNIKOVA, . STRAND, C. ZETTERSTRÖM, A. WAHLGREN, O. SÖDER | |
| Su | ımmary | . 255 |
| 1. | Introduction | . 256 |
| 2. | The role of androgens in male fetal differentiation | . 256 |
| 3. | Functions of the fetal Leydig cell | . 258 |
| 4. | Impact of endocrine disrupters on male reproductive health | . 259 |
| 5. | Effects of environmental anti-androgens on the reproductive development and hormonal functions of Leydig cells | . 260 |
| | 5.1. Procymidone | |
| | 5.2. Linuron. | |
| | 5.3. Vinclozolin | |
| | 5.4. p,p' DDT and its derivatives | . 263 |
| 6. | Effects of phthalates on Leydig cell function and reproductive development | 264 |
| 7. | Effects of dioxin on androgen production by Leydig cells | |
| | and on reproductive health | 265 |
| 8. | Effects of endocrine disrupters on adrenal function | 266 |
| 9. | Effects of endocrine disrupters on the hormonal functions of ovarian cells | 268 |
| 10 | . Endocrine disrupters, inflammation and androgen production | 271 |
| 11 | . Conclusions | 273 |
| Ac | knowledgements | 274 |
| Re | ferences | 274 |
| | | |
| | NVIRONMENTAL IMPACT ON CONGENITAL DISEASES: | |
| | HE CASE OF CRYPTORCHIDISM. WHERE ARE WE NOW, NO WHERE ARE WE GOING? | |
| | F. THONNEAU, E. HUYGHE AND R. MIEUSSET | |
| | mmary | 281 |
| | Background | |
| | Has the incidence of cryptorchidism increased? | |
| | Increasing evidence of a link between various male reproductive health issues | |
| ٥. | increasing evidence of a fink between various male reproductive health issues | 285 |

| 4. | Toxi | c effect of anti-androgenic compounds on male reproductive health | .286 |
|----|-------|--|-------|
| | 4.1. | | |
| | | production in testis and male reproductive tract development | .286 |
| | 4.2. | T (2.2.2.) | .287 |
| | 4.3. | | 200 |
| _ | | with anti-androgenic effects | |
| 5. | | ted data on environmental impact of cryptorchidism in humans | |
| | | DES | |
| | | Epidemiological studies (occupational and environmental conditions). | |
| | | Bioaccumulation of chemical compounds | |
| | | re do we go from here, and how can we answer the question? | |
| Re | feren | ces | .291 |
| | | | |
| | | ONMENTAL RISK AND SEX RATIO IN NEWBORNS | |
| M. | PET | ERKA, Z. LIKOVSKY AND R. PETERKOVA | |
| Su | mmaı | -y | . 295 |
| 1. | Intro | duction | . 296 |
| 2. | Basi | ic manifestations of developmental damage | .297 |
| | | Lethality - prenatal loss | |
| | | Major malformations | |
| | | 2.2.1. Prenatal extinction of major malformations | .300 |
| | | Minor malformations usually manifest as functional defects | |
| | | Intrauterine growth retardation and low birth weight | |
| 3. | Dose | response in teratology | . 302 |
| | 3.1. | Substances with teratogenic and lethal effects | . 303 |
| | 3.2. | | |
| | 3.3. | Substances with neither a teratogenic nor a lethal effect | . 304 |
| 4. | Resid | dual teratogenesis and the epidemiology of malformations | . 304 |
| 5. | Sex | ratio | . 306 |
| | 5.1. | Sex determination | .306 |
| | 5.2. | Newborn sex ratio | |
| | 5.3. | Newborn sex ratio and the vulnerability of male embryos/fetuses | . 307 |
| 6. | Cher | nobyl | . 309 |
| | 6.1. | Radioactive clouds and whole body radioactivity | . 309 |
| | 6.2. | Newborn sex ratio – November 1986 | |
| | 6.3. | Critical period for radiation | . 311 |
| | 6.4. | Hypothesis about the reasons for the selective abortion of male | |
| | | fetuses after the Chernobyl disaster | |
| 7. | Conc | clusion | .313 |
| Re | feren | CAC | 313 |

SECTION 4: COUNTRY REPORTS

| CONGENITAL ABNORMALITIES IN GREECE: FUNCTIONAL EVALUATION OF STATISTICAL DATA 1981 – 1995 | |
|--|-----|
| E BRILAKIS E FOUSTERIS AND J. PAPADOPULOS | |
| Summary | 323 |
| 1. Introduction | 324 |
| 2. Method | 325 |
| 3. Results | 326 |
| 4. Discussion | 334 |
| 4.1. Specific mortality and infant mortality ratios | 334 |
| 4.2 Variations of the ratios within Greece | 335 |
| 4.3 Hospitalisation due to birth defects within Greece | 336 |
| 4.4. Deaths/hospitalisation ratio due to births defects in Greece | 336 |
| 5. Conclusions | |
| References | 337 |
| | |
| CONGENITAL ANOMALIES IN BULGARIA | |
| E. TERLEMESIAN AND S. STOYANOV | |
| Summary | 339 |
| 1. Introduction | |
| 2. Congenital diseases in Bulgaria: The Sofia register database | |
| 3. Mortality rates | |
| 4. Discussion | |
| 5. Conclusions | |
| References | |
| References | 555 |
| CONGENITAL ANOMALIES IN THE BRITISH ISLES | |
| J. RANKIN | |
| Summary | 250 |
| • | |
| 1. Introduction | |
| 1.1. Recording of congenital anomalies in the British Isles | |
| 1.1.1. The national congenital anomaly system | |
| 1.1.2. Regional congenital anomaly registers | |
| 1.1.3. Disease-specific registers | |
| 1.1.4. The British Isles network of congenital anomaly registers | |
| 2. Variations in the prevalence of congenital anomalies in the British Isles | |
| 2.1. Secular trends in congenital anomaly prevalence | 368 |
| 2.2. Regional variations in congenital anomaly prevalence | 369 |

| 3. Use of data from congenital anomaly registers in environment and health research in the British Isles |
|--|
| 3.1. Cluster investigations |
| 3.1.1. Geographical variation in congenital anomaly rates |
| 4. Conclusion |
| Acknowledgements |
| References |
| references |
| EUROPEAN UNION-FUNDED RESEARCH ON ENDOCRINE DISRUPTERS AND UNDERLYING POLICY |
| T. KARJALAINEN |
| Summary |
| 1. Introduction |
| 1.1. Path to adoption of community strategy for endocrine disrupters380 |
| 1.2. Community strategy for endocrine disrupters381 |
| 1.2.1. Short-term strategy |
| 1.2.2. Medium-term strategy |
| 1.2.3. Long-term strategy |
| 2. European Commission-sponsored research on endocrine disrupters |
| 2.1. Research activities in the fourth research framework programme |
| (1994-1998) |
| (FP5: 1998-2002) |
| 2.2.1. Key-action 4: environment and health |
| 2.2.2. Projects funded by the Energy, Environment and Sustainable |
| Development (EESD) thematic programme |
| 2.3. Research activities in the sixth framework programme of research (FP6: 2002-2006) |
| 2.3.1. Outcome of first, second, and third calls for proposals396 |
| 3. Research activities in the seventh framework programme of research (FP7: |
| 2006-2013) |
| 4. Conclusion |
| References404 |
| |
| SECTION 5: CONCLUSIONS |
| ENVIRONMENTAL IMPACTS ON CONGENITAL ANOMALIES - INFORMATION FOR THE NON-EXPERT PROFESSIONAL |
| L. HENS |
| Summary |

TABLE OF CONTENTS

| 1. | Introduction | -10 |
|-----|---|----------------|
| 2. | Problem identification | 12 |
| 3. | Methodological approaches4 | 14 |
| | 3.1. Clinical evidence 4 3.2. Epidemiological evidence 4 3.3. Evidence from experimental developmental toxicology 4 | 17 24 |
| | 3.4. Evidence from wildlife studies | |
| | Mechanisms causing congenital anomalies | |
| | 5.1. Advising in the public health sector | 34 35 35 |
| 6. | Discussion and conclusions | |
| Re | ferences4 | 43 |
| LIS | ST OF ABBREVIATIONS4 | 51 |
| LI | ST OF UNITS4 | 55 |
| IN. | DEX4 | 57 |